CENTRAL NERVOUS CONTROL OF CARDIAC ACTIVITY (*PART I*)*

By

S. K. MANCHANDA

Department of Physiology,

All-India Institute of Medical Sciences, New Delhi.

INTRODUCTION

In engineering controls are employed to direct the behaviour of a man-made system usually termed as a plant. A system, according to Grodins (25) is a collection of interacting components subject to disturbances and exhibiting a certain behaviour as illustrated in figure 1A. Controls can be introduced in this system to regulate its behaviour (figure 1B). In case

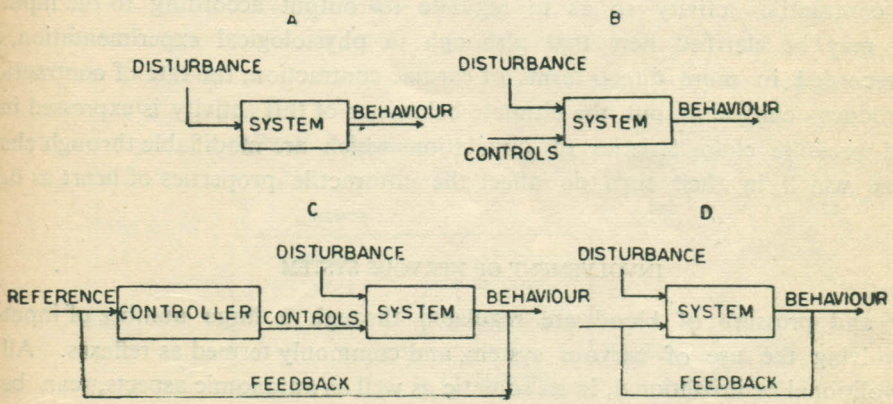

Fig. 1

Block-diagram explaining the principles underlying the control mechanisms employed in various engineering system.

it is desirable to make this regulation automatic, the controls are made dependent in some way on the system's behaviour so that errors in this behaviour at any moment are detected by the controller through a continuous flow of the feedback information. The controller then modifies the controls to bring the changed behaviour back to the normal levels. Included in this scheme, therefore, is also the provision of a reference framework of "normal levels" which the controller continuously consults so as to direct its controls appropriately (figure 1C). A

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feedback control system which is thus designed to compensate disturbance is generally called
regulator.

CARDIAC CONTROLS

Controls employed for the regulation of biological phenomena can be analysed wit
advantage on a similar plane. The system that is heart expresses its behaviour by pumpin
blood into body's arterial bed at a determined flow rate and perfusion pressure. The bloo
perfusing the tissues is brought back to the heart via the venous channels for re-pumping
This pumping action of the heart thus interposes itself in a closed system of blood circulatio
At any moment it so adjusts its activity that the input into the heart (venous return) is equa
to its output (cardiac output). It is possible to control the input-output adjustments throug
the innate mechanisms located in the heart itself (figure 1D). For example, if due to an
disturbance in the system the input into the heart increases, the resultant increased distensio
of cardiac musculature leads to an increased force of ventricular contraction (Starling's Law)
Similarly increased input also causes an increased distension of the atria leading to a further
excitation of the pacemaker tissue thereby increasing the heart rate. Consequently output o
the heart per unit time is increased (Bainbridge Effect). In both cases the heart strives t
modify its contractile activity so as to regulate its output according to the input that it
receives. It may be clarified here that although in physiological experimentation, cardiac
activity is recorded in more direct terms of cardiac contraction, the rate of contraction, and
their final product - cardiac output, the ultimate behaviour of this activity is expressed in terms
of flow and pressure characteristics of circulation which are modifiable through changes in
vascular tone which in their turn do affect the contractile properties of heart as described
above.

INVOLVEMENT OF NERVOUS SYSTEM

Flow and pressure of blood are regulated through a large number of input-output
systems involving the use of nervous system, and commonly termed as reflexes. All animal
behaviour, volitional or involitional, in its somatic as well as autonomic aspects, can be analy-
sed on the basis of these reflexes. It is in this context that a rather confusing array of reflexes
has so far been identified. For a proper understanding of these reflex mechanisms, it is best
perhaps to classify them into (a) the ones which essentially aim at stabilizing the system and
(b) the ones which strive to achieve a dynamic response by mobilizing the cardiovascular
activities in a determined pattern for bodily needs at a particular moment.

HOMEOSTATIC OR STABILIZING REFLEXES

An oft-quoted example of these reflexes is the carotid sinus reflex which aims at pro-
viding a moment to moment regulation of arterial blood pressure. In the classical concept
carotid sinus stretch receptors are continuously sampling the pressure of blood flowing through
the sinus. Increase in sinus pressure leads to an increased impulse discharge in the sinus
nerve which is conveyed to the cardiovascular centres in the medulla oblongata. These centres

in turn control the activity of autonomic nerves supplying the heart and blood vessels. Increased barrage of sinus nerve impulses in the medulla oblongata inhibits the sympathetic discharge and excites the vagal fibres which together decrease the heart rate and its force of contraction thus reducing the cardiac output. Simultaneous arteriolar dilatation because of sympathetic inhibition diminishes the peripheral resistance. The blood pressure which varies with the product of cardiac output and peripheral resistance is thus brought down. Decreased cardiac output is balanced by a decrease in venous return which is achieved by the simultaneous venodilatation and the resultant pooling of blood in the capacity vessels. Carotid sinus reflex in this way achieves an automatic and continuous regulation of blood pressure. Figure 2 depicts schematically the pathway of this reflex and translates it in terms of the control theory as enunciated above. Carotid sinus reflex first described by Hering in 1923 is only one of many such mechanisms which aim primarily at stabilzing the system's behaviour. A large number of reflexes originating from the specialized receptors (mechano and chemoreceptors)

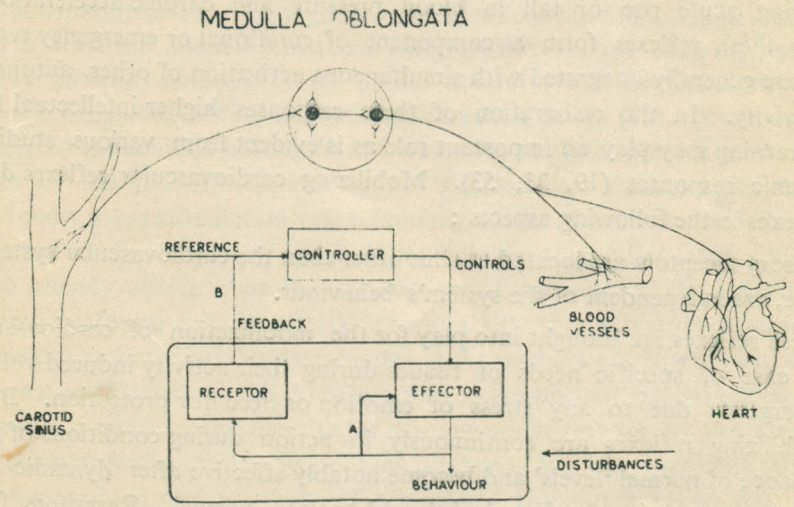

Fig. 2

Carotid sinus reflex as an example of the stablising reflexes. Inset explains it on the basis of a regulatory control system as implied in the control theory. Heart is the effector organ which produces behaviour expressed in terms of arterial pressure and flow of blood. Variations in the 'pressure-behaviour' are sensed by the sinus stretch receptors. The sinus nerve carries this information in the form of sensory impulses to the controller suposed to be localized at the medullary level (Feedback B) which modifies the controls by changing the activity of autonomic nerves supplying the heart and blood vessels. An automatic regulatory control is thus obtained which stabilized the system's behaviour with references to the levels set under resting conditions in any individual.

Feedback A of the system's behaviour into the effector itself signifies the innate control system of the heart which adjusts the second parameter of its behaviour i.e. the flow of blood. The heart modifies its output according to the input that it receives by employing the principles of Starling and Bainbridge. The control systems are therefore, comples and built one round the other.

located in blood vessels and heart have been documented. Excellent reviews of the investigations dealing with the detailed work-out of different components of each of these reflexes have been published (4, 27). While the Starling's Law and Bainbridge's effect provide the mechanisms aimed at producing adjustments of total volume of blood flowing in and out of the

heart, these reflexes adjust the cardiac and vascular behaviour so as to maintain a particul level of perfusion pressure and flow in different circulatory beds. The reference for this lev essentially conforms to what is present when the body is in an average resting condition The local regulations and these reflex regulations, therefore, in essence constitute the homeo static or stabilizing control mechanisms.

HOMEODYNAMIC OR MOBILIZING REFLEXES

The disturbances in the system's behaviour with regard to perfusion pressure and bloo flow can be created at various levels of reflex behaviour originating from receptors located a sites other than those which are involved in the stabilization of system's behaviour. Refle cardiovascular effects are obtainable on the excitation of all cutaneous exteroceptors an muscle proprioceptors (16, 24, 35, 57). Thus excitation of receptors by heat, cold, pain an muscle stretch can all lead to a variety of cardiovascular responses. Besides, visceral afferent (61) auditory, visual and olfactory activation in special circumstances results in autonomi reflexes involving acute rise or fall in blood pressure and cardiac acceleration or slowing Physiologically these reflexes form a component of emotional or emergency reactions of th organism and are generally integrated with simultaneous activation of other autonomic as wel as somatic activity. In the elaboration of these responses higher intellectual functions like memory and learning may play an important role as is evident from various studies of condi tioned autonomic responses (19, 23, 53). Mobilizing cardiovascular reflexes differ from th stabilizing reflexes in the following aspects :

1. Sensory receptors are located at sites other than the cardiovascular system and there fore, are independent of the system's behaviour.
2. These reflexes are brought into play for the mobilization of cardiovascular activity in case of specific needs of tissues during their activity induced volitionally or in emergency due to any stress of emotion or need for protection. By contrast the stabilizing reflexes are continuously in action during conditions of rest for main tenance of normal 'levels' and become notably effective after dynamic reactions are over so as to bring the disturbed 'levels' back to normal. Receptors for stabilizing reflexes perhaps do get activated during emergency, but under these circumstances mobilizing reflexes have an over-riding influence on the cardiovascular parameters.
3. The mobilizing controls are a complex of open loop systems originating from receptors located far and wide and operating at various levels of central nervous system depending upon the complexity of somatic-autonomic coupling involved under any circumstance. The controls are not regulatory for the cardiovascular activities because no feedback is available to them from the heart and blood vessels. They primarily serve to adjust the cardiovascular activities for the regulation of other functions of the body as in temperature regulation, muscular exercise, etc. In comparison the stabilizing controls are automatically regulated through a com plex of closed loop feedback systems and seem to operate only at the most basic level of the central nervous system i.e. the brain stem.

CONTROLS BY THE CENTRAL NERVOUS SYSTEM

Role of the central nervous system is that of a controller which receives information from various sources of autonomic and somatic origin and transforms it into executive signals which so affect the cardiovascular activities that the special requirements of the body at any particular condition of rest or of activity are met with.

DEVELOPMENT OF CURRENT CONCEPTS

Classical concepts of the C. N. S. mechanisms controlling the cardiovascular activity owe their origin in the main, to those studies which were aimed at localizing the cardiovascular centres in the medulla oblongata. Dittmar in 1870 showed that stimulation of cut central end of sciatic nerve induces a good reflex rise in arterial pressure even after separation of medulla from the rest of brain and therefore propounded the presence of vasoconstrictor centres in the medulla oblongata (17). Dittmar later, employing the descending serial sections of brain showed that arterial pressure remained practically unaffected till a section was made at the caudal limit of superior fovea. Subsequent caudal sections led to more and more fall in blood pressure till a level of about 4 mm above the obex was reached when the pressure reached as low a level as is generally obtained in the spinal animal (18). Owsjannikow reached similar conclusions with his studies having the same experimental design (46). Ranson and Bellingsley in 1916 stimulated the medulla oblongata and were able to find pressor and depressor points on the floor of the fourth ventricular (51). Ranson also demonstrated that pressor reflex obtained on sciatic nerve stimulation was essentially mediated from the medulla oblongata and that spinal cord really had very insignificant role in this reflex (50). Meanwhile Claude Bernard had already shown that the transection of the cord at any cervical level causes an immediate and profound fall in arterial pressure (9). Later, various authors correlated the cardioaccelaratory and cardio-inhibitory centres in the medulla oblongata with the pressor and depressor areas respectively (7, 15, 31, 43). This was sufficient ground for Bayliss to expound the existence of a primary integrative site for cardiovascular reflexes in the medulla oblongata (8). These cardiovascular centres were then mapped out by pinpointed stimulations in the medulla oblongata of cat with the help of stereotaxic techniques (1, 44, 59). Similar results were obtained in the sheep (2). In general these studies localize the vaso-constrictor and cardio-acceleratory points in the more rostral and lateral parts of the pontomedullary reticular formation and vasodilator and cardioinhibitory points in the more medial and caudal parts of the medullary reticular formation. It had already been shown that pressor reflex of sciatic origin is essentially mediated from regions higher than the spinal cord (50), while newer electrophysiological studies demonstrated that brain regions higher than the brain stem were not necessary for the elicitation of baroreceptor reflexes (12). These studies thus led to the concept that there is a primary control centre in the medulla oblongata which mediates the reflex cardiovascular activities and that there are two functional divisions of this control area:- the vasoconstrictor-cardioaccelaratory centre, activation of which leads to increased sympathetic discharge and inhibition of vagal impulses, and vasodilator-cardioinhibitory area whose activation leads to a decrease in the sympathetic discharge, and an increase in the vagal

activity. These two divisions are considered to have reciprocal connections with each other. Sensory impulses from baroreceptors and chemoreceptors essentially flow to these areas which in turn subserve to grade the sympathetic and parasympathetic motor discharges in various patterns according to the quality and quantity of sensory information that is received. Spinal cord is of secondary importance and plays its part only in the spinal animal. Though a number of studies were available which reported the cardio-vascular effects on stimulation of hypothalamus (33, 49, 52) and higher regions of brain (3, 28, 32, 58), medullary reticular formation continued to reign supreme as the primary controller of cardiovascular reflexes. By far the most respectable evidence in this respect came from Bronk and his colleagues (12, 49) who demonstrated by electrophysiological recording of the impulse discharges of the cardiac sympathetic nerves that the reflex rhythmic discharges induced in these nerves by low frequency stimulation of the femoral nerves continued to be elicited after the removal of hypothalamus. Further they showed that the sympathetic discharges were inhibited when systemic arterial pressure

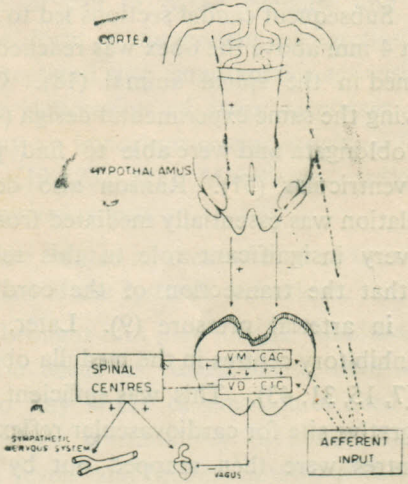

Fig. 3

Schematic diagram detailing the current concepts of Cardiovscular controls. VM = Vasomotor centre, CAC = Cardioaccelerator centre, VD = Vasodilator centre and CAC = Cardioinhibitor centre. VM and CAC; and VD and CIC respectively are coupled together on a comon morphological basis in th medulla oblongata.

The medullary centres are considered to have an over-riding influence on the spinal centres and thus change the activity of autonomic nerves under the bombarment of sensory inputs of various types from periphery and higher nervous system.

More recent physiological and morphological studies however, demonstrate that these concepts are insufficient to contain all the observable cardio-vascular phenomena, and at best are rather vague.

was raised, presumably through the baroreceptor reflexes. This sympathetic inhibition was still achievable after the removal of hypothalamus. The concept as evolved so far implied that medulla oblongata is capable of providing adequate tonic maintenance and reflex regulation of cardiovascular function and supramedullary regions of forebrain, limbic system and neocortex exert quite profound added influences whenever there is a situation of emotion or exertion as evoked from these higher regions which then affect this basic regulation appropriately so as to adjust the autonomic parameters with the somatic activities (figure 3).

RECENT ADVANCES

Extensive work has been done on the regulatory aspects of cardiovascular system during the last few decades. Literature has been thoroughly reviewed in a number of excellent articles (20, 29, 47, 48). In these pages therefore only those works will be dealt which have a direct bearing on the concepts of cardiovascular regulations.

THE MEDULLARY CENTRES

It has been reported that the midbrain or the bulbopontine animal does show a moderate decline in the mean arterial pressure (34, 48, 60). The animals with hypothalamic lesions show a persistant fall in the mean arterial pressure (41). These observations signify that some tonicity to cardiovascular function is also imparted by the regions higher than the medulla oblongata. Manning later (42) showed that hypothalamus can mediate baroreceptor reflexes independent of the medulla oblongata because carotid occlusion responses could still be elicited after massive lesions in the medulla oblongata and in these preparations with medullary lesions, the occlusion responses disappeared after a section at the midbrain level. Bhattarai and Manchanda (10) have demonstrated that high midbrain section does not lead to a fall in mean arterial pressure. But if the sections are below this level, arterial pressure does fall and the amount of fall depends on the amount of reticular formation eliminated. The animals which do not show a fall in pressure, may be maintaining it by compensatory influences from the baroreceptors which can be convincingly demonstrated by comparing the magnitude of afferent discharges before and after the midbrain section. This later aspect has not been reported in the literature so far. Stimulation studies have shown that there is a continuity of morphological substratum from medulla to midbrain and hypothalamus which can elicit equally potent vasopressor and vasodepressor reponses alongwith the increase or decrease in heart rate and its force of contraction (37, 38, 42).

While considering the integrative functions of the medullary cardiovascular centres one often forgets that these centres are essentially a part of the total reticular formation of brain stem which extends from the bulb a little above the decussation of pyramids at the caudal end to the sub-cortical nuclei in the forebrain cephalically (21). The bewildering complexity of these neuronal networks has been discussed by Brodal in their morphological as well as functional aspects (11). He points out that though there are several nuclei in the reticular formation which differ with respect to their cytoarchitecture, fibre connections and intrinsic organization, these nuclei are essentially dependent on each other since their fibre connections provide ample possibilities for interaction and collaboration between various regions. The Scheibels (56) have demonstrated the presence of reticular neurones of various dimensions and profuse arborizations. Neurones having processes extending from diencephalon to spinal cord have also been identified. Medullary reticular formation therefore, cannot be isolated from the rest of the brainstem.

Further it should be understood that the so-called 'cardiovascular functions' form a part of the total organismal activity. As Brodal says "In actual life these diverse *funct* are inter-related in various ways and scarecely ever take place in isolation. Nature does necessarily work in these terms of functions which we have set up as working tools in attempts to understand biological problems" (11). Reticular formation gets its afferent c nections from all the sensory systems and makes to and fro connections with different br structures at various levels of the C.N.S. (22). It is, therefore, able to regulate the entire ra of somatic and visceral activities of the body. The relative literature has been excelle summed up in Magoun's monograph (39). Neurophysiologists who have stimulated the br stem structures know that the so-called cardiovascular points also produce simultane responses affecting somatic and respiratory activities. As a matter of fact this couplin various systems was reported by Bach in 1948 who found parallel changes in arterial pressu respiration and knee jerk on localized stimulations within the bulbar facilitatory and inhibit areas (5). Amoroso *et al.* (2) working on sheep also indicated the existence of diverse neuro pools in which vasomotor and respiratory neurones are quite intermingled (2). Manchanda a Kaul have recently shown that the stimulation of a point in the so-called "vasopressor are can produce various patterns of blood flow, venous tone, heart rate and respiration which m or may not be accompanied by the increase in mean arterial pressure (40). Bard had earl discussed the problem whether the hindbrain cardiovascular areas are a part and parcel of t well known facilitatory and inhibitory systems of the brainstem reticular formation or not a emphasized the difficulties in correlating the various visceral and somatic responses obtained c stimulation of reticular formation (6).

Studies on the electrophysiology of relevant brainstem neurones have been report recently. "Cardiovascular" neurones firing with heart beat or with changes in arterial pressu were identified by Salmoiraghi in 1962 (54). It has now been demonstrated that carotid ner stimulation produces short lateny evoked potentials in the nucleus tractus solitarius and lon latency potentials in both medial and lateral reticular formation (30,55). Crill and Reis (196 have reported that stimulation of nucleus tractus solitarius and medial reticular formation ca evoke antidromic activity in the carotid nerve (14). A further detailed report from Reis laboratory establishes the presence of short latency monosynaptic evoked responses in thes regions on carotid nerve stimulation. These authors identified long latency responses in th dorsolateral regions of both medullary and pontine reticular formation in various subnucle (45). Gunn *et al.* (26) have demonstrated that the vagal cardiomotor mechanisms in the hindbrains of dog and cat operate mainly through the nucleus ambiguous and not through the dosral motor nucleus (29).

It seems therefore, that these "buffer" fibres make connections of the first order in the so-called depressor area and that polysynaptic integrating connections are available not only in the dorsolateral medullary reticular formation (the classical pressor area) but also are extended

into the pontine reticular formation. Though data about the sensory projections from the cardiovascular reflexogenic areas at the mesencephalic and hypothalamic level is not available, possibility of polysynaptic connections at these levels cannot be overestimated.

So far direct electrophysiological studies demonstrating the influence of receptors located at sites other than the cardiovascular reflexogenic zones have not been reported. Considering the fact that the homeodynamic or mobilizing reflexes form an important part of the cardiovascular activities of a normally living individual, the impinging of signals from a wide variety of receptors on this neurological substratum can however, be expected. Review of literature brings home to us that researches in cardiovascular regulations have been particularly attuned towards the problems of constancy of "milieu interiuer" or "homeostasis". Therefore, one finds that while a vast majority of workers have devoted their attention to the stabilizing mechanisms like the barostatic or chemostatic reflexes, the homeodynamic mechanisms which are concerned in the main with the mobilization of caridovascular activities have remained comparatively ignored. Burn's (13) study of the respiratory neurones is highly instructive in this respect. He has shown that if the "respiratory region" in the medulla oblongata is completely isolated from all ascending, descending and cranial nerve connections, there is a significant reduction in the number of active respiratory neurones (13).

An advantage of the application of neurophysiological techniques to the problems of cardiovascular regulation has been that the regulation physiologist has now started approaching the subject from the point of view of reflex arcs as envisaged in the details of modern morphological studies. It is in this context, and as is revealed from the evidence given above, that the classical concept of medullary depressor and pressor zones needs to be abandoned in favour of a more widespread reticular substratum extending from the caudal part of medulla to the mesencephalon having the basic mechanisms for producing a large variety of patterns of cardiovascular activities in response to a wide variety of sensory input coming from the spinal cord and the cranial nerves. With such an approach, it may not be far when sufficient studies will be available which will put the cardiovascular regulation on the same firm footing as the regulation of somatic activities.

Viewing the problems in this context, the controversy of what is more important for the tonic drive of cardiovascular activities : medulla or hypothalamus, becomes meaningless. The function of providing inhibitory and facilitatory tonic drive and its automatic control through the stabilizing reflexes can be easily attributed to the whole of reticular formation. The discrepancies of the "serial section" experiments of various investigators can be explained on the basis of the amount of reticular tissue left available after the section. The idea of the role of residual tissue quantity in the function take-over is not new (36). (*To be concluded*)

where ?